REMARKS

The Specification has been revised to correct an obvious typographical error in the amino acid sequence length of MT-MDH (338 vs. 294).

I. Comments regarding restriction requirement and claim objections

Claims 14, 15, 16, 28 and 29 are "method of use" claims which all depend from the product claims 3 and 12. Therefore, upon allowance of product claims 3 and 12, the method of use claims 14, 15, 16, 28 and 29 should be rejoined and considered together, in accordance with the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products.

It is believed that the above amendments address the Examiner's concerns regarding claim dependency. Withdrawal of the objections concerning such matters is therefore believed to be in order.

II. Rejections for lack of utility under 35 U.S.C. §101 and §112

Embodiments of the present invention are directed, *inter alia*, to polynucleotides encoding mitochondrial malate dehydrogenase (MT-MDH). In particular embodiments, the mitochondrial malate dehydrogenases are selected from among amino acid sequences comprising SEQ ID NO:1. These polypeptides have strong chemical and structural homology with known mitochondrial malate dehydrogenases. For example:

> MT-MDH is 338 amino acids in length and has two potential N-glycosylation sites at residues N-117 and N-145, seven potential casein kinase II phosphorylation sites at T-54, S-69, T-109, T-170, S-261, S-309, and S-310, four potential protein kinase C phosphorylation sites at residues T-213, T-227, S-326, and T-336, a mitochondrial malate dehydrogenase active site signature between residues V-169 and V-181, and a transit peptide sequence from residues M-1 to N-24. As shown in Figures 2A and 2B, MT-MDH has chemical and structural homology with murine mitochondrial mitochondrial malate dehydrogenase (GI 56643; SEQ ID NO:3) and porcine mitochondrial mitochondrial malate dehydrogenase (GI 164541; SEQ ID NO:4). In

particular, MT-MDH and murine mitochondrial mitochondrial malate dehydrogenase share 94% identity, share both potential N-glycosylation sites, six potential casein kinase II sites, three potential protein kinase C sites, the mitochondrial malate dehydrogenase active site signature, and the transit peptide sequence. As illustrated by Figures 3A and 3B, respectively, MT-MDH and murine mitochondrial mitochondrial malate dehydrogenase (SEQ ID NO:3) have similar isoelectric points (pI = 8.8). As illustrated by Figures 4A and 4B, MT-MDH contains potential NAD(H) and NADP(H) binding site motifs. Northern analysis shows the expression of this sequence in various libraries, at least 49% of which are immortalized or cancerous and at least 24% of which involve immune response. Of particular note is the expression of MT-MDH in fetal tissues; in cardiovascular, gut, nervous, and reproductive tissues; and in secretory and hematopoietic tissues. (Specification at page 14, line 29 to page 15, line 17)

Claims 3-7, 9, 10, 12 and 13 have been rejected under 35 U.S.C. §101 and §112, first paragraph, based on the allegation that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." In particular the Examiner asserts that "There is no real disclosed or real world utility associated with the nucleac acids of SEQ ID NO:2 or the protein of SEQ ID NO:1. (12/17/02 Office Action, at page 4)

Applicants respectfully traverse this rejection. As described supra, embodiments of the invention at issue include a polynucleotide sequence corresponding to a gene that is expressed in humans including "in fetal tissues; cardiovascular, gut, nervous, and reproductive tissues; and in secretory and hematopoietic tissues." (Specification at page 15, lines 15 -17). Further, the claimed polynucleotide encodes a polypeptide demonstrated in the patent specification to be a member of the mitochondrial malate dehydrogenase family, whose biological functions include the catalytic conversion of malate to pyruvate (See the Specification, for example, at page 2 lines 17-21). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this response the declaration of Dr. Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The

Bedilion Declaration demonstrates that the positions and arguments made by the Office Action with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes in particular how the claimed expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as highly specific probes in a cDNA microarray:

> Persons skilled in the art [in September 1997] would appreciate that cDNA microarrays that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating developmental, vesicle trafficking, immunological and neoplastic disorders for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15)

The Office Action does not dispute that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring applications. Instead, the Office Action contends that the claimed polynucleotides cannot be useful without precise knowledge of their biological functions, or the biological functions of their encoded polypeptide. However this rejection is erroneous as there is no basis in law for knowledge of biological function to prove utility. In fact just the opposite, as the courts have held that "[i]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir.1999); Newman v. Quigg, 877 F.2d 1575, 1581, 11 U.S.P.Q.2d 1340, 1345 (Fed. Cir. 1989). It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

As demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to the precise function of the protein encoded by them. The uses of the claimed polynucleotides in gene expression monitoring applications are in fact independent of their precise biological functions.

I. The Applicable Legal Standard

To meet the utility requirements of 35 U.S.C. § 101 and, derivatively, § 112, first paragraph, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 U.S.P.Q. 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 U.S.P.Q. 689 (1966). As held by the court in a recent case in the Court of Appeals for the Federal Circuit, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 U.S.P.Q. 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 U.S.P.Q.2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 U.S.P.Q.2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 U.S.P.Q.2d 1094 (Fed. Cir. 1991) the United States Court of Appeal for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 U.S.P.Q. 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Clearly, this threshold has been met by virtue of the Bedilion declaration. Further, only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it (see *In re Cortright*, 165 F.3d 1353, 1357, 49 U.S.P.Q.2d 1464; *In re Brana*, 51 F.3d 1560, 1566; 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995)). In that case the Patent Office bears the burden to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Ids.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 U.S.P.Q. 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility (see *Brana*, 51 F.3d at 1566). The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

However contrary to the requirements in case law described *supra*, the Examiner's 35 U.S.C. §101 rejection in the instant Office Action fails to demonstrate either that the Applicants' assertions of utility are legally insufficient or that a person of ordinary skill in the art would reasonably doubt that they could be achieved. For these reasons alone the rejections should be withdrawn.

II. Use of the claimed polynucleotides for diagnosis of conditions or diseases characterized by expression of MT-MDH, for toxicology testing, and for drug discovery are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of MT-MDH for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Patent Examiner. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotide.

The instant application was a divisional application of and claims priority to United States Patent Application Serial No. 08/922,957 filed on 09/03/1997 (hereinafter "the Bandman '957 application"), both having the identical specification.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Bandman '957 application on September 3, 1997 would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, *e.g.*, as a highly specific probe for the expression of that specific polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotide in cDNA microarrays of the type first developed at Stanford University for

evaluating the efficacy and toxicity of drugs, as well as for other applications. (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that the "Bandman '957 application would have led a person skilled in the art on September 3, 1997 who was using gene expression monitoring in connection with working on developing new drugs for the treatment of developmental, vesicle trafficking, immunological and neoplastic disorders to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [have appreciated on September 3, 1997] that cDNA microarrays that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than cDNA microarrays that did not contain the polynucleotides in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for treating developmental, vesicle trafficking, immunological and neoplastic disorders for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre-September 3, 1997 publications showing the state of the art on September 3, 1997. (Bedilion Declaration, ¶ ¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on September 3, 1997 (and for several years prior to September 3, 1997) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be evaluated in connection

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Bandman '957 specification, that the claimed polynucleotide would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

with the development of the drug" and how the teachings of the Bandman '957 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Bandman '957 application at the time it was filed "would have wanted their cDNA microarray to have a [SEQ ID NO:1-encoding polynucleotide probe] because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to September 3, 1997." (Bedilion Declaration, ¶ 15, item (f)) This, by itself, provides more than sufficient reason to compel the conclusion that the Bandman '957 application disclosed to persons skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotide.

Nowhere does the Patent Examiner address the fact that, as described on pages 41-42 of the Bandman '957 application, the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed polynucleotide is known to be expressed in humans, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. (*see Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983), ("When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. 101 is clearly shown."); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); MPEP § 2107 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., <u>they are useful in analyzing compounds</u>)" (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating developmental, vesicle trafficking, immunological and neoplastic disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed in fetal, cardiovascular, gut, nervous, reproductive, secretory and hematopoietic tissues and in tissues associated with developmental, vesicle trafficking, immunological and neoplastic disorders (see the Bandman '957 application at page 15, lines 15-17), there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about developmental, vesicle trafficking, immunological and neoplastic disorders and drug candidates or potential toxins with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The Bedilion Declaration shows that a number of pre-September 3, 1997 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Bandman '957 application was filed (Bedilion Declaration ¶¶ 10-14; Bedilion Tabs A-G). Indeed, Brown and Shalon's U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Tab D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Bedilion Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Bedilion Tab D at col. 15, lines 13-18 and 52-58 and col. 18, lines 25-30).

Literature reviews published shortly after the filing of the Bandman '957 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
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> * * *
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> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
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> * * *
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> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. (emphasis added)

Rockett et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems and potential, 29 Xenobiotica No. 7, 655 (1999).

In another pre-September 3, 1997 article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. The amplicons can also be used directly by, for example, arraying onto glass for expression analysis, for DNA binding assays, or for any direct DNA assay.

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, 94 Proc. Nat. Acad. Sci. 8945 (Aug. 1997) (emphasis added).

B. The use of human polynucleotides and their encoded polypeptides as tools for toxicology testing, drug discovery, and the diagnosis of disease is "well-established"

The technologies made possible by expression profiling and the DNA and polypeptide tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Dr. Bedilion in his declaration.

Toxicology testing is used in both drug development and safety assessment. Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett, et al., Differential gene expression in drug metabolism and toxicology: practicalities, problems, and potential, Xenobiotica 29(7):655, 656 (1999):

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs.

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and Toxicology: The Advent of Toxicogenomics, 24 Molecular Carcinogenesis 153 (1999); Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology -- potentials and limitations, 112-13 Toxicology Letters 467 (2000).

Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected

> for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome

proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA Arrays to Toxicology, 107 Environ. Health Perspec.681, No. 8 (1999). Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator on the Nuwaysir paper, Dr. Cynthia Afshari, to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding, indicating that even the expression of carefully selected control genes can be altered. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The

implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Patent Examiner failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the Examiner's rejections should be overturned regardless of their merit.

C. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 U.S.P.Q.2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 U.S.P.Q. 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequence and millions of other sequences throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

III. The Patent Examiner's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotide are not "specific and substantial" utilities. (12/17/02 Office Action, at page 3). The Examiner is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility.

The Patent Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise biological "function/activity" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Examiner would require, in addition, that the Applicant provided a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Examiner would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15, Bedilion), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO

guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Examiner has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Examiner should have looked first to the benefits it is alleged to provide.

B. Because the uses of polynucleotides encoding MT-MDH in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention has substantial utility.

The PTO rejected the claims at issue on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the PTO's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office has recognized that just because an invention is used in a research setting does not mean that it lacks utility (MPEP § 2107):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified utility and inventions whose specific utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the PTO's Training Materials themselves to be useful, as well as DNA sequences used, for example, as markers.

Only a limited subset of research uses are not "substantial" utilities: those in which the only known use for the claimed invention is to be an **object** of further study, thus merely inviting further research. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945 ("What Applicants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines."). Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete. (Bedilion Declaration at ¶ 15.)

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include uses such as diagnostic assays (e.g., pages 36-44).

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to overturn the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the

final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at p.52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.")).

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus, incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have

found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. *See Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § II.B.2 (*Montedison,* 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions that heretofore have been considered to be patentable and that have indisputably benefitted the public, including the claimed invention. *See supra* § II.B. Thus the Training Materials cannot be applied consistently with the law.

V. To the extent the rejection of the patented invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

III Written description rejections under 35 U.S.C. §112, first paragraph

Claims 3-7, 9, 10, 12 and 13 were rejected under 35 U.S.C. §112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art the inventor(s) at the time the application was filed, had possession of the claimed invention." (12/17/02 Office Action, at page 4) This rejection is respectfully traversed.

In order to expedite prosecution, and solely for purpose thereof, Applicants have amended Claim 1 such that polynucleotides encoding biologically active or immunogenic fragments of SEQ ID NO:1 are no longer recited. Therefore, the rejection as it pertains to polynucleotides encoding biologically active or immunogenic fragments of SEQ ID NO:1 is moot. Also, solely for purposes of expediting prosecution, Applicants have canceled claim 13, thus the rejection as it pertains to the subject matter of claim 13 is now moot.

In making the rejection, the Office Action has further asserted that:

> There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to described additional representative species of these polynculeotides by any identifying structural characteristics or properties for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently disclose the invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. (12/17/02 Office Action, at page 4-5).

This rejection is improper, as the claims define subject matter which is described in the Specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed subject matter at the time the application was filed. The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law:

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991).

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics[42] which provide evidence that applicant was in possession of the claimed invention,[43] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[44] What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.[45] If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.[46]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1 and SEQ ID NO:2.

The subject matter encompassed by claims 3-7, 9, 10, 12 and 13 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 3 recites a polynucleotide encoding "a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1" and the "variant" language of independent claim 12 recites "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:2."

The amino acid sequence of SEQ ID NO:1 and the polynucleotide sequence of SEQ ID NO:2 are explicitly disclosed in the specification. See, for example, the Sequence Listing. Variants of SEQ ID NO:1 and SEQ ID NO:2 are described in the Specification at, for example, page 4, lines 13-14; page 7, lines 4-7 and 12-18; and page 15, lines 18-27

One of ordinary skill in the art would recognize polynucleotide sequences which are variants having a polynucleotide sequence at least 95% to SEQ ID NO:2, or which encode polypeptide variants having an amino acid sequence at least 95% identical to SEQ ID NO:1. Given any naturally occurring

polynucleotide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:2, or whether it encoded a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited polynucleotide variants of SEQ ID NO:2 and polynucleotides encoding polypeptide variants of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 U.S.P.Q.2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 U.S.P.Q.2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than on functional characteristics. For example, the "variant language" of independent claim 12 recites chemical structure to define the claimed genus:

> 12. An isolated polynucleotide selected from the group consisting of: .....
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:2,....

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an

important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action fails to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope. In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding mitochondrial malate dehydrogenases, including polynucleotides encoding mitochondrial malate dehydrogenases related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as mitochondrial malate dehydrogenases and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding a polypeptide comprising "a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 338 amino acid residues). This variation is far less than that of polynucleotides encoding all potential mitochondrial malate dehydrogenases related to SEQ ID NO:1, i.e., those mitochondrial malate dehydrogenases having as little as 30% identity over at least 150 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of September 3, 1997. Much has happened in the development of recombinant DNA technology in the 18 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base the written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately

described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be withdrawn.

IV. Enablement Rejection under 35 U.S.C. § 112, first paragraph

Claims 3-7, 9, 10, 12 and 13 stand rejected under 35 U.S.C. 112, first paragraph allegedly for lacking an enabling disclosure with respect to variants and biologically active and immunogenic fragments of SEQ ID NO:1. The Examiner has specifically stated that "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." (12/17/02 Office Action, at page 5) This rejection is respectfully traversed.

In order to expedite prosecution, and solely for purpose thereof, Applicants have amended Claim 1 such that polynucleotides encoding biologically active or immunogenic fragments of SEQ ID NO:1 are no longer recited. Therefore, the rejection as it pertains to polynucleotides encoding biologically active or immunogenic fragments of SEQ ID NO:1 is moot. Also, solely for purposes of expediting prosecution, Applicants have canceled claim 13, thus the rejection as it pertains to the subject matter of claim 13 is now moot.

In making the rejection, the Examiner has specifically contended that

> "The specification does not provide guidance with respect to the specific structural/catalytic amino acids and the structural motifs essential for enzyme structure and activity function which cannot be altered. Thus searching for the specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in a polynucleotide is well outside the realm of routine experimentation and predictability in the art" (12/17/02 Office Action, at page 6)

The first paragraph of 35 U.S.C. §112 requires that the Specification describe how to make and use the claimed subject matter. That requirement has been met in the present application. In particular, the Specification describes how to make and use naturally-occurring polypeptide variants of SEQ ID NO:1 and polynucleotides encoding such variants.

Independent claim 3 recites not only that the "variant" polynucleotides encode polypeptides that are at least 95% identical to SEQ ID NO:1, but also have "***a naturally-occurring amino acid sequence***." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of MT-

MDH) and SEQ ID NO:2 (the polynucleotide sequence encoding MT-MDH), one of skill in the art would be able to routinely obtain a polynucleotide encoding a polypeptide comprising "a naturally-occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1." Likewise for the "variant" polynucleotides defined by independent claim 12: "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 95% identical to the polynucleotide sequence of SEQ ID NO:2." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. For example:

> The terms "stringent conditions"or "stringency", as used herein, refer to the conditions for hybridization as defined by the nucleic acid, salt, and temperature. These conditions are well known in the art and may be altered in order to identify or detect identical or related polynucleotide sequences. Numerous equivalent conditions comprising either low or high stringency depend on factors such as the length and nature of the sequence (DNA, RNA, base composition), nature of the target (DNA, RNA, base composition), milieu (in solution or immobilized on a solid substrate), concentration of salts and other components (e.g., formamide, dextran sulfate and/or polyethylene glycol), and temperature of the reactions (within a range from about 5°C below the melting temperature of the probe to about 20°C to 25°C below the melting temperature). One or more factors be may be varied to generate conditions of either low or high stringency different from, but equivalent to, the above listed conditions. (Specification at page 13, lines 11-21)
>
> In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding MT-MDH or closely related molecules, may be used to identify nucleic acid sequences which encode MT-MDH. The specificity of the probe, whether it is made from a highly specific region, e.g., 10 unique nucleotides in the 5' regulatory region, or a less specific region, e.g., especially in the 3' coding region, and the stringency of the hybridization or amplification (maximal, high, intermediate, or low) will determine whether the probe identifies only naturally occurring sequences encoding MT-MDH, alleles, or related sequences. (Specification at page 37, line 25 to page 38, line 3)
>
> Probes may also be used for the detection of related sequences, and should preferably contain at least 50% of the nucleotides from any of the MT-MDH encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and derived from the nucleotide sequence of SEQ ID NO:2 or from genomic sequence including promoter, enhancer elements, and introns of the naturally occurring MT-MDH. (Specification at page 38, lines 4-8)
>
> See also Example VI, at page 50.

Thus, one skilled in the art need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:1. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already

exist in nature. By adjusting the nature of the probe or nucleic acid (*i.e.*, non-conserved, conserved or highly conserved) and the conditions of hybridization (maximum, high, intermediate or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims. Furthermore, the Specification sets forth an assay for measuring malate dehydrogenase activity (Example X at page 52, lines 11-18).

Accordingly, the document cited by the Examiner relating to structure-function relationships in proteins is simply not germane to whether one can make and use the polypeptide variants recited by the present claims [*i.e.*, Attwood et al. (Comput. Chem., 25(4):329-339, 2001)]. Likewise, the cited document relating to alleged difficulties in assigning protein function based on homology comparison is not relevant to making the claimed polynucleotide variants [*i.e.*, Ponting (Brief. Bioinform., 2(1):19-29, 2001)]. That is, regardless of the precise functional characteristics of the SEQ ID NO:1 and SEQ ID NO:2 variants, one can still make the claimed polynucleotide variants using the disclosure provided by the present Specification. The polynucleotides could then be used in, for example, diagnostic testing, drug discovery, expression profiling, etc., as discussed in the Bedilion Declaration.

Furthermore, the Examiner's attention is also directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

Claim 3 recites, *inter alia*, a polynucleotide encoding a polypeptide comprising "a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1." In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as MT-MDH proteins and which have as little as 30% identity over at least 150 residues to SEQ ID NO:1. The "95% variants" recited by the present claims have a variation that is far less than that of all potential MT-MDH proteins related to SEQ ID NO:1, i.e., those MT-MDH proteins having as little as 30% identity over at least 150 residues to SEQ ID NO:1. Therefore, one would expect the SEQ ID NO:1 variants recited by the present claims to have the functional activities of a MT-MDH protein.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 ***requires nothing more than objective enablement.*** [emphasis added] How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be take as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited variants of SEQ ID NO:1 or SEQ ID NO:2. Hence, a *prima facie* case for non-enablement has not been established with respect to the variants of SEQ ID NO:1 or SEQ ID NO:2.

For at least the above reasons, withdrawal of this rejection is requested.

V Rejections under 35 U.S.C. §102

Claim 3 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Joh *et al.* Applicants respectfully traverse this rejection. In order to expedite prosecution and solely for purposes thereof, Applicants have amended part b of claim 1 to recite "a naturally occurring polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1". Joh *et al.* does not describe such a polynucleotide. Withdrawal of the rejection is therefore requested.

Claim 13 stands rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Hudson. Applicants have canceled claim 13. Accordingly, withdrawal of the rejection is respectfully requested..

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Please charge Deposit Account No. **09-0108** in the amount of $110.00 as set forth in the enclosed fee transmittal letter for a month extension of time. If the USPTO determines that additional fees are necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 14, line 29 to page 15, line 17 has been amended as follows:

MT-MDH is [294] 338 amino acids in length and has two potential N-glycosylation sites at residues N-117 and N-145, seven potential casein kinase II phosphorylation sites at T-54, S-69, T-109, T-170, S-261, S-309, and S-310, four potential protein kinase C phosphorylation sites at residues T-213, T-227, S-326, and T-336, a mitochondrial malate dehydrogenase active site signature between residues V-169 and V-181, and a transit peptide sequence from residues M-1 to N-24. As shown in Figures 2A and 2B, MT-MDH has chemical and structural homology with murine mitochondrial mitochondrial malate dehydrogenase (GI 56643; SEQ ID NO:3) and porcine mitochondrial mitochondrial malate dehydrogenase (GI 164541; SEQ ID NO:4). In particular, MT-MDH and murine mitochondrial mitochondrial malate dehydrogenase share 94% identity, share both potential N-glycosylation sites, six potential casein kinase II sites, three potential protein kinase C sites, the mitochondrial malate dehydrogenase active site signature, and the transit peptide sequence. As illustrated by Figures 3A and 3B, respectively, MT-MDH and murine mitochondrial mitochondrial malate dehydrogenase (SEQ ID NO:3) have similar isoelectric points (pI = 8.8). As illustrated by Figures 4A and 4B, MT-MDH contains potential NAD(H) and NADP(H) binding site motifs. Northern analysis shows the expression of this sequence in various libraries, at least 49% of which are immortalized or cancerous and at least 24% of which involve immune response. Of particular note is the expression of MT-MDH in fetal tissues; in cardiovascular, gut, nervous, and reproductive tissues; and in secretory and hematopoietic tissues.

IN THE CLAIMS:

Claim 1, 2, 8, 11, 13, 17 and 18 have been canceled.

Claims 3, 4, 9 and 12 have been amended as follows:

3. (Amended) An isolated polynucleotide encoding a polypeptide [of claim 1] selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, and

b) a polypeptide comprising a naturally occurring amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO:1.

4. (Amended) An isolated polynucleotide [encoding a polypeptide of claim 2] of claim 3 which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:1 .

9. (Amended) A method for producing a polypeptide [of claim 1] encoded by a polynucleotide of claim 3, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide [encoding the polypeptide] of claim [1] 3, and

b) recovering the polypeptide so expressed.

12. (Amended) An isolated polynucleotide [comprising a sequence] selected from the group consisting of:

a) a polynucleotide comprising [a]the polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising a naturally occurring [polynucleotide comprising a] polynucleotide sequence at least [90%] 95% identical to [a] the polynucleotide sequence of SEQ ID NO:2,

c) a polynucleotide having a sequence complementary to a polynucleotide of a),

d) a polynucleotide having a sequence complementary to a polynucleotide of b) and

e) an RNA equivalent of a)-d).